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Original Article

Lower risk for cardiovascular mortality in oral 1α-hydroxy vitamin D_3 users in a haemodialysis population

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Abstract

Background. Renal failure results in deficiency of active vitamin D_3 that has diverse effects on metabolism and organ functions. Treatment with active forms of vitamin D_3 ameliorates abnormalities in bone and mineral metabolism, cardiac function, immune response and others. We hypothesized that treatment with vitamin D_3 may be beneficial for survival in patients with end-stage renal disease (ESRD).

Methods. We compared the risk of death between regular users ($n = 162$) and non-users ($n = 80$) of oral 1α-hydroxyvitamin D_3 (alfacalcidol) in a cohort of ESRD patients undergoing haemodialysis for a follow-up of 61 ± 23 months. The daily dose of alfacalcidol ranged from 0.25 to 1.5 μg, with a median of 0.5 μg.

Results. The alfacalcidol users showed a lower risk of death from cardiovascular disease than the non-users in a univariate Cox model [hazards ratio (HR) 0.287, 95% confidence interval (CI) 0.127–0.649, $P = 0.003$], whereas the risk for death from non-cardiovascular disease was not different between the two groups. Stepwise multivariate Cox analysis showed that cardiovascular mortality was significantly associated with age, presence of diabetes mellitus and treatment with alfacalcidol (HR 0.377, 95% CI 0.246–0.578, $P = 0.022$).

Conclusions. These results indicate that use of oral alfacalcidol was associated with reduced risk for cardiovascular death in this cohort of ESRD patients. The result of this observational study warrants further randomized controlled trials with 1α-hydroxy vitamin D_3 to confirm the possibility that such medication improves survival of ESRD patients.

Keywords: cardiovascular mortality; end-stage renal disease; haemodialysis; vitamin D_3

Introduction

Renal failure impairs activation of 25-hydroxyvitamin D by 1α-hydroxylation in renal tissue. The classic target tissues of 1,25-dihydroxyvitamin D (calcitriol) are the intestine, kidneys, parathyroid glands and bone. In addition, there are numerous tissues that contain receptors for vitamin D (VDRs) such as the immune system, the heart, arteries, endocrine organs, the liver, the brain and others [1]. Because of the broad tissue distribution of VDRs, vitamin D deficiency in renal failure has been attributed to various manifestations of uraemia [2] such as impaired bone and mineral metabolism, cardiovascular complications and suppressed immune functions. In fact, there are reports showing that treatment with active forms of vitamin D_3 improved these abnormalities [3,4]. On the other hand, toxic effects of vitamin D have been demonstrated by studies using experimental animals and cell culture systems [5]. Of particular concern is the possibility that treatment with vitamin D increases calcium × phosphorus product and may result in vascular calcification [6] and worse outcomes [7]. Although a recent study by Teng *et al.* [8] showed that survival rate was different between two groups of haemodialysis patients, one receiving calcitriol and the other receiving paricalcitol, a new vitamin D analogue having smaller effects on serum calcium and phosphate, their study does not answer the question of whether to treat, or not to treat, with some forms of vitamin D in view of survival

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advantage in haemodialysis patients. Thus, the overall benefit of treatment with vitamin D in ESRD is not established. The Japanese Society for Dialysis Therapy analysed the association between the use of vitamin D_3 and 1-year survival in 77 486 haemodialysis patients among whom 4584 patients died during 1998 [9]. After adjustment for age, gender, haemodialysis duration and diabetes mellitus, the relative risk of overall mortality was 0.760 ($P < 0.0001$) for the vitamin D_3 users compared with non-users, suggesting a potentially beneficial effect of vitamin D_3 on survival. This observation needs to be confirmed. In addition, it is an important question whether treatment with vitamin D_3 has favourable effects on cardiovascular death, since cardiovascular disease is the most important cause of death in the dialysis population. In the present study, we addressed this question by comparing the outcomes of regular users and non-users of oral 1α-hydroxyvitamin D_3 (alfacalcidol) in a prospective cohort of 242 patients with end-stage renal disease (ESRD) undergoing haemodialysis.

Subjects and methods

Study design and subjects

This is an observational study in a cohort consisting of 242 haemodialysis patients, approved by the ethical committee at Inoue Hospital. The underlying renal diseases were diabetic nephropathy ($n = 55$) and non-diabetic origins ($n = 187$). They received 3–5 h haemodialysis, three times a week, using bicarbonate dialysate at Inoue Hospital, Suita, Japan. The registration and baseline studies of the subjects were done in 1992.

Based on the medications at entry, 162 patients were identified as regular vitamin D users and the remaining 80 patients as non-users. Alfacalcidol was the only oral vitamin D that was prescribed in this hospital at the time of entry. The daily dose of alfacalcidol ranged form 0.25 to 1.5 μg with a median of 0.5 μg. Clinical characteristics of the users and non-users of alfacalcidol are summarized in Table 1. The group of vitamin D_3 users had lower non-high-density lipoprotein (HDL)-cholesterol, fewer diabetic patients and fewer patients with ischaemic heart disease (IHD) than the non-user group. IHD was diagnosed when a subject had one or more of the following criteria: (i) past history of percutaneous coronary intervention or coronary artery bypass grafting; (ii) presence of significant stenosis by coronary angiography; (iii) presence of ST–T abnormalities on electrocardiogram associated with typical symptoms attributable to angina pectoris; and (iv) use of one or more medications for coronary ischaemia. Sufficient baseline information was not available for stroke, amputations or malignancies. No one had a history of parathyroidectomy before entry into the study.

Biochemical assays and other measurements

We measured haematocrit, serum calcium, phosphorus, blood urea nitrogen, serum creatinine, total and HDL-cholesterol by routine laboratory methods using non-fasting blood obtained just before starting a haemodialysis session. Non-HDL-cholesterol was calculated by subtracting HDL-cholesterol from total cholesterol. Smoking status, presence of diabetes mellitus and presence of IHD were based on careful history taking. Carotid artery intima-media thickness

Table 1. Baseline characteristics of the users and non-users of 1α-hydroxyvitamin D_3

	Alfacalcidol users	Non-users	*P*-value
No. of patients	162	80	–
Age (years)	55.5 ± 10.8	56.5 ± 10.3	0.815
Male gender (%)	56%	48%	0.203
Smokers (%)	47%	39%	0.287
Systolic BP (mmHg)	149 ± 22	149 ± 22	0.893
Diastolic BP (mmHg)	80 ± 10	79 ± 9	0.731
Non-HDL-cholesterol (mg/dl)	119 ± 34	136 ± 40	0.0007
HDL-cholesterol (mg/dl)	37.3 ± 11.8	38.3 ± 13.2	0.567
Diabetes mellitus (%)	18%	31%	0.019
Presence of IHD (%)	10%	20%	0.043
Duration on HD (months)	91 ± 71	91 ± 69	0.960
Calcium (mg/dl)	9.14 ± 0.65	9.03 ± 0.68	0.192
Phosphorus (mg/dl)	5.81 ± 1.10	5.89 ± 1.22	0.638
Calcium × phosphorus (mg^2/dl^2)	53.2 ± 10.5	53.4 ± 12.5	0.906
HS-PTH (ng/ml)	8.5 (0.3–79.7)	7.2 (0.3–98.0)	0.471
CA-IMT (mm)	0.89 (0.56–5.91)	0.97 (0.58–4.62)	0.165
Carotid artery calcification (%)	15%	18%	0.292
BUN (mg/dl)	81 ± 16	81 ± 18	0.815
Creatinine (mg/dl)	11.8 ± 2.2	11.3 ± 2.3	0.100
Haematocrit (%)	27.8 ± 4.5	27.3 ± 3.9	0.346
BMI (kg/m^2)	21.3 ± 2.7	21.5 ± 2.9	0.202

Prevalence was given as a percentage, and the difference in prevalence between the two groups was evaluated by χ^2 test. Continuous variables were summarized as mean ± SD, and difference between the groups was assessed by analysis of variance. For continuous variables with skewed distribution, data were summarized as median (range), and the difference between the groups was tested using non-parametric Mann–Whitney *U*-test.

BP, blood pressure; HDL, high-density lipoprotein; IHD, ischaemic heart disease; HD, haemodialysis; HS-PTH, parathyroid hormone by a high sensitivity assay; CA-IMT, carotid artery intima-media thickness; BUN, blood urea nitrogen; BMI, body mass index.

(CA-IMT) was measured by high-resolution B-mode ultrasonography using a real-time ultrasonograph with a 10 MHz in-line Sectascanner (SSD 650 CL, Aloka Co. Ltd, Tokyo, Japan) as described previously [10]. The carotid artery was scanned bilaterally in the longitudinal and transverse projections. The examination included ~4 cm of the common carotid artery, the carotid bulb and 1 cm each of the internal and external arteries. The greatest thickness of intima-media complex, including plaque if present, was used for analysis. The presence of carotid artery calcification was defined as the presence of high-echoic intimal lesions with typical acoustic shadow.

Statistical methods

Data were summarized as mean ± SD for continuous variables. The difference between mean values was assessed by analysis of variance. Data with a skewed distribution, such as serum parathyroid hormone (PTH) and CA-IMT, were summarized as median (range), and comparison between groups was performed by non-parametric Mann–Whitney *U*-test. Prevalence was compared by χ^2 test. Survival curves were estimated by the Kaplan–Meier method followed by log-rank test. Prognostic variables for survival were examined using univariate and multivariate Cox proportional hazards regression models. *P*-values < 0.05 were considered significant. All these analyses were performed using statistical software (StatView 5, SAS Institute Inc., Cary, NC) for Windows personal computers.

Results

Outcome of the subjects

The follow-up was finished in December, 1998. During the follow-up, 19 cases were censored because they had moved away. The censored cases were not statistically different from the other cohort members in terms of age at entry, gender, duration of haemodialysis, percentage of diabetics, pre-existing IHD and the use of alfacalcidol. We recorded 53 deaths including 31 fatal cardiovascular events. The remaining 170 patients were alive on haemodialysis. The mean (± SD) follow-up period was 61 ± 23 months. Date and cause of death were obtained by reviewing the hospital record forms. The 31 deaths from cardiovascular events were attributable to coronary heart disease ($n = 5$), cerebrovascular disease ($n = 4$), congestive heart failure ($n = 10$) and sudden death ($n = 12$). Sudden death was defined as a witnessed death that occurred within 1 h after the onset of acute symptoms, with no evidence of accident or violence. The remaining 22 deaths were due to infectious disease ($n = 11$), cancer ($n = 3$), hepatic failure ($n = 2$), bleeding ($n = 1$) and others ($n = 5$).

Adherence to the alfacalcidol treatment

Although we could not collect data on medications during the whole study period, we were able to obtain information on vitamin D treatment during the first 2 years of the study period. Sixty-three percent of the alfacalcidol users remained on the medication during the 2 years, whereas 56% of the non-user group never received alfacalcidol in that period. Other subjects received alfacalcidol for some time during the 24 months. Based on the calculation of patient-months, the vitamin D_3 users group received the medication for 20.6 out of 24 months (85%), and the non-users group did not receive alfacalcidol for 21.1 out of 24 months (88%).

Comparison of outcomes between the users and non-users of alfacalcidol

According to the Kaplan–Meier analysis (Figure 1), the alfacalcidol users showed a significantly lower risk for

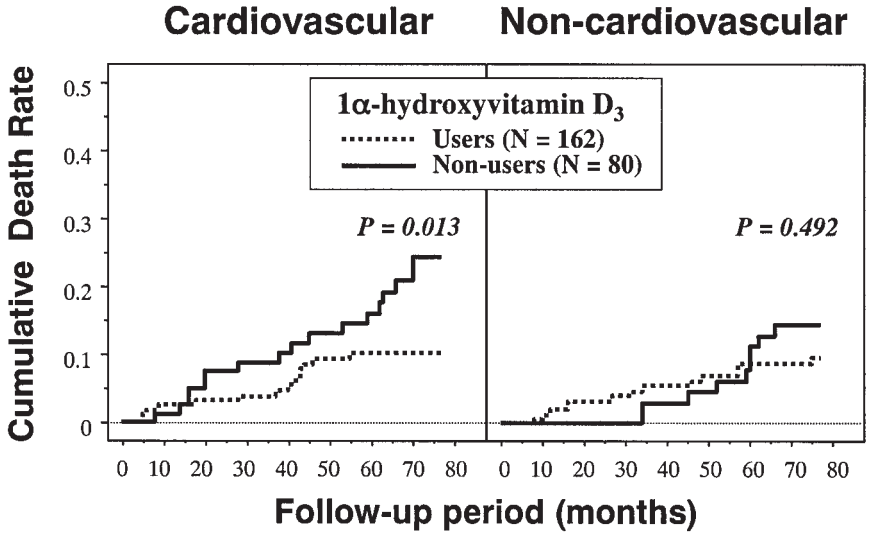

Fig. 1. Kaplan–Meier analysis of association of use of 1α-hydroxyvitamin D_3 and risk of death from cardiovascular and non-cardiovascular causes in a cohort of 242 haemodialysis patients. The difference in the survival curves between the two groups was assessed by log-rank test.

death from cardiovascular disease than the non-users, whereas the risk for non-cardiovascular mortality was not different between the two groups.

Predictors of cardiovascular mortality by univariate Cox analysis

The univariate Cox proportional hazards model was used to examine univariate predictors of cardiovascular death (Table 2). This analysis confirmed the significant association between use of alfacalcidol and cardiovascular mortality. Other significant univariate predictors were age, systolic blood pressure, non-HDL-cholesterol, presence of diabetes mellitus and CA-IMT. Presence of IHD and presence of carotid artery calcification were predictive of cardiovascular death at borderline significance.

Independent predictors of cardiovascular death in multivariate Cox analysis

Table 3 shows the result by the multivariate Cox analysis using the stepwise procedure. Age and the presence of diabetes mellitus were indicated as independent predictors of cardiovascular mortality, whereas the use of alfacalcidol was associated with a significantly reduced risk of cardiovascular death independent of these factors. The favourable impact of the use of alfacalcidol on cardiovascular mortality remained significant when the model included systolic blood

Table 2. Univariate predictors of cardiovascular mortality by univariate Cox analysis

Candidate variables	HR (95% CI)	*P*-value
Age (per 1 year)	1.071 (1.028–1.115)	0.001
Gender (male *vs* female)	1.397 (0.627–3.110)	0.413
Smoking (smoker *vs* non-smoker)	1.426 (0.650–3.126)	0.376
Systolic BP (per 1 mmHg)	1.029 (1.005–1.053)	0.016
Diastolic BP (per 1 mmHg)	1.015 (0.973–1.059)	0.489
Non-HDL-cholesterol (per 1 mg/dl)	1.012 (1.003–1.022)	0.012
HDL-cholesterol (per 1 mg/dl)	0.999 (0.967–1.031)	0.935
Diabetes mellitus (presence *vs* absence)	5.915 (2.667–13.12)	<0.0001
Presence of IHD (presence *vs* absence)	2.292 (0.914–5.750)	0.077
Duration of haemodialysis (per 1 month)	0.995 (0.989–1.001)	0.128
Serum calcium (per 1 mg/dl)	0.734 (0.414–1.301)	0.289
Phosphorus (per 1 mg/dl)	0.985 (0.693–1.400)	0.931
Ca × P product (per one point)	0.991 (0.956–1.028)	0.628
HS-PTH (higher *vs* lower)	0.617 (0.277–1.374)	0.238
CA-IMT (>0.92 mm *vs* <0.92 mm)	2.374 (1.024–5.506)	0.044
CA calcification (presence *vs* absence)	2.346 (0.979–5.621)	0.056
BUN (per 1 mg/dl)	1.019 (0.995–1.043)	0.121
Creatinine (per 1 mg/dl)	0.953 (0.790–1.149)	0.614
Haematocrit (per 1%)	0.961 (0.870–1.062)	0.441
BMI (per 1 kg/m^2)	1.013 (0.882–1.163)	0.855
Use of alfacalcidol (users *vs* non-users)	0.287 (0.127–0.649)	0.003

Association between cardiovascular mortality and each candidate variable was analysed using a univariate Cox proportional model. The table gives hazards ratios (HRs) and 95% confidence intervals (95% CIs) with statistical significance (*P*-value). The cut-off levels for HS-PTH (8.3 ng/ml) and CA-IMT (0.92 mm) were the median levels.
BP, blood pressure; HDL, high-density lipoprotein; HS-PTH, parathyroid hormone by a high sensitivity assay; CA-IMT, carotid artery intima-media thickness; BUN, blood urea nitrogen; BMI, body mass index.

Table 3. Independent predictors of cardiovascular mortality by stepwise multivariate Cox analysis

Step	Independent factors	HR (95% CI)	*P*-value
1	Diabetes mellitus (presence *vs* absence)	3.705 (2.406–5.709)	0.002
2	Use of alfacalcidol (users *vs* non-users)	0.377 (0.246–0.578)	0.022
3	Age (per 1 year)	1.055 (1.030–1.079)	0.020
	Global model significance		<0.0001
Variables not selected			
	Systolic BP (per 1 mmHg)	–	0.156
	Carotid artery calcification (presence *vs* absence)	–	0.182
	Non-HDL-cholesterol (per 1 mg/dl)	–	0.207
	Presence of IHD (presence vs absence)	–	0.802
	CA-IMT (>0.92 mm *vs* <0.92 mm)	–	0.934

Independent predictors of cardiovascular death were evaluated by the stepwise multivariate Cox proportional hazards model. The result at the final step is shown.
HR, hazards ratio; 95% CI, 95% confidence interval; BP, blood pressure; non-HDL, non-high-density lipoprotein; IHD, ischaemic heart disease; CA-IMT, carotid artery intima-media thickness.

pressure, non-HDL-cholesterol, pre-existence of IHD, CA-IMT or carotid artery calcification as the fourth forced covariate (data not shown).

Discussion

The present results show that the use of the active vitamin D_3 derivative alfacalcidol was associated with a significantly lower risk for cardiovascular mortality in this cohort of haemodialysis patients. To our knowledge, this is the first report that suggests the potentially protective effect of alfacalcidol therapy against cardiovascular mortality in patients with ESRD.

There are several possibilities to explain the current finding. First, treatment with alfacalcidol may improve cardiac function. Although we did not measure cardiac function, administration of vitamin D has been reported to improve cardiac performance in haemodialysis patients [11] either by suppressing PTH secretion or via a vitamin D-dependent mechanism. Such treatment could reverse impaired cardiac function due to hyperparathyroidism by correcting increased intracellular calcium [3].

Secondly, vitamin D_3 treatment may suppress myocardial hypertrophy. Calcitriol has been shown to antagonize endothelin-stimulated hypertrophy in neonatal rat cardiomyocytes [12]. Vitamin D deficiency and increased plasma endothelin in renal failure may therefore promote cardiac hypertrophy. Park *et al*. [13] showed that intravenous calcitriol administration produced a significant regression of left ventricular mass index and concomitant reductions in plasma PTH, angiotensin II and atrial natriuretic peptide (ANP), one of the earliest markers of cardiac hypertrophy.

Thirdly, vitamin D_3 may favourably affect arterial cells. We previously showed that macrophage scavenger receptor expression is suppressed by $1,25(OH)_2$ vitamin D_3 [14]. The effects of calcitriol on vascular smooth muscle cells are biphasic, and both the deficiency and excess of vitamin D_3 stimulate proliferation of vascular smooth muscle cells [15,16]. Therefore, the dose and plasma concentration of active forms of vitamin D_3 may influence the overall effect on arterial cells. It is important to note that the patients in this study received a relatively low dose (median 0.5 μg per day) of alfacalcidol.

Fourthly, treatment with vitamin D_3 may improve the lipid profile directly or indirectly by affecting calcium, PTH and other factors. Hypocalcaemia and hyperparathyroidism in uraemia are closely related to reduced activities of lipoprotein-regulating enzymes [17]. In haemodialysis patients, oral calcitriol treatment increased apolipoprotein A-I and HDL-cholesterol with a concomitant decrease in PTH [18].

Finally, improved immune functions by treatment with vitamin D_3 [4] may increase the defence against oxidized lipoproteins. The serum titre of anti-oxidized low-density lipoprotein (LDL) antibody shows an inverse association with CA-IMT in healthy subjects [19]. A low titre of antibody against oxidized low-density lipoprotein is an independent predictor of increased risk of cardiovascular death in haemodialysis patients [20].

It may appear strange that the alfacalcidol users and non-users had almost identical serum calcium, phosphate and PTH levels at entry. However, these baseline data were not pre-treatment values but levels achieved by use of alfacalcidol and other pharmacological and non-pharmacological manipulations. Since we found the beneficial effects of alfacalcidol on the immune response in haemodialysis patients [4], it has been our policy to prescribe low-dose alfacalcidol for haemodialysis patients who do not have hypercalcaemia or severe hyperphosphataemia. It is a likely explanation that the alfacalcidol users had lower pre-treatment levels of calcium and phosphate than the non-users, and the treatment with alfacalcidol increased calcium and phosphate. Otherwise, a higher delivered dose of haemodialysis in the alfacalcidol users might have reduced serum phosphate levels, eventually leading to prolonged survival.

There are several limitations to the present findings. First, some variables in the baseline study were different between the alfacalcidol users and non-users, such as the proportion of diabetic subjects, the presence of IHD and the non-HDL-cholesterol level. However, the association between the use of alfacalcidol and a lower risk of cardiovascular death remained significant after adjustment for these factors. Secondly, because this was not a randomized controlled study, we cannot rule out the possibility that the outcome difference may have been due to factors that we could not analyse, such as serum C-reactive protein, albumin, Kt/V, and use of angiotensin-converting enzyme inhibitors, β-blockers, aspirin, phosphate binders and other medications. Therefore, the finding of this study needs to be confirmed by randomized controlled studies. Thirdly, we could not detect a significant impact of other risk factors such as plasma lipids, calcium, phosphate, blood pressure, arterial wall thickness and calcification in multivariate analysis. This may be due to the limited number of fatal events, and/or being based on the single point measurements rather than mean levels of multiple point measurements. Fourthly, although we included sudden death in cardiovascular death, it might have overestimated the true cardiovascular mortality rate in this cohort. Takeda *et al*. [21] reported that the group of sudden death included death from non-cardiovascular origin such as infectious disease (17.8%) and malignancies (15.1%). Finally, we did not monitor the plasma level of $1,25(OH)_2$ vitamin D. If its plasma level is of predictive value, we will be able to identify patients to treat and the dose of alfacalcidol to use more efficiently.

In conclusion, the present study showed that cardiovascular mortality was lower in haemodialysis patients who took oral alfacalcidol at the clinical dosage, suggesting that this treatment may improve the outcome of the patients. Clearly, further randomized and controlled studies are needed to confirm the

potentially beneficial effect of alfacalcidol in patients with ESRD.

Conflict of interest statement. None declared.

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